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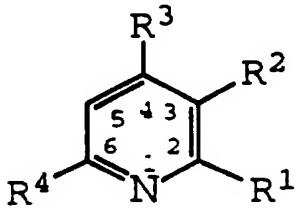
(54) Title: 3,4-DIARYL SUBSTITUTED PYRIDINES FOR THE TREATMENT OF INFLAMMATION

(57) Abstract

A class of substituted pyridyl compounds is described for use in treating inflammation and inflammation-related disorders. Compounds of particular interest are defined by formula (I), wherein R^1 is haloalkyl; wherein R^2 is aryl optionally substituted at a substitutable position with one or more radicals independently selected from alkylsulfinyl, alkyl, cyano, carboxyl, alkoxycarbonyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, halo, alkoxy and alkylthio; wherein R^3 is aryl substituted at a substitutable position with a radical selected from alkylsulfonyl and sulfamyl; and wherein R^4 is selected from halo, alkoxy and alkynyloxy; or a pharmaceutically-acceptable salt thereof.



(I)

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3,4-DIARYL SUBSTITUTED PYRIDINES FOR THE TREATMENT OF INFLAMMATION

FIELD OF THE INVENTION

This invention is in the field of antiinflammatory pharmaceutical agents and specifically relates to compounds, compositions and methods for treating inflammation and inflammation-associated disorders, such as arthritis.

BACKGROUND OF THE INVENTION

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG_2, PGH_2 and PGE_2, has been a common target of antiinflammatory drug discovery. However, common non-steroidal antiinflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 (COX-2)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more

effectively reduces inflammation and produces fewer and less drastic side effects.

The references below that disclose antiinflammatory activity, show continuing efforts to find a safe and effective antiinflammatory agent. The novel pyridines disclosed herein are such safe and also effective antiinflammatory agents furthering such efforts. The invention's compounds are found to show usefulness in vivo as antiinflammatory agents with minimal side effects. The substituted pyridinyl compounds disclosed herein preferably selectively inhibit cyclooxygenase-2 over cyclooxygenase-1.

Pyridines have been described for various uses, including the treatment of inflammation.

U.S. Patent No. 3,655,679, to Shen et al, describes monoaryl substituted pyridine carboxylic acids as having antiinflammatory activity.

British Patent No. 1,238,959 describes 3-aryl substituted pyridyl derivatives as having antiinflammatory activity.

U.S. Patent No. 4,011,328, to Pinhas et al, describes derivatives of 2,3-diaryl-pyridine-3-acetic acid as having antiinflammatory properties.

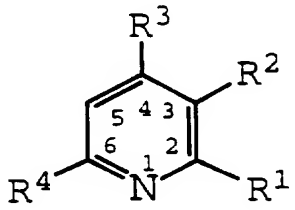
U.S. Patent No. 5,004,743, to Young et al, describes mono-aryl substituted pyridyl compounds as having anti-inflammatory properties.

U.S. Patent No. 5,169,857, to Angerbauer et al, describes pyridines as useful in the treatment of hyperproteinaemia or arteriosclerosis. Specifically, 2,6-dimethyl-4-(4-fluorophenyl)-5-phenyl-pyridines are described.

The invention's pyridyl compounds are found to show usefulness *in vivo* as antiinflammatory agents with minimal side effects.

DESCRIPTION OF THE INVENTION

A class of substituted pyridyl compounds useful in treating inflammation-related disorders is defined by Formula I:



(I)

wherein R^1 is haloalkyl;

wherein R^2 is aryl optionally substituted at a substitutable position with one or more radicals independently selected from alkylsulfinyl, alkyl, cyano, carboxyl, alkoxycarbonyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, halo, alkoxy and alkylthio;

wherein R^3 is aryl substituted at a substitutable position with a radical selected from alkylsulfonyl and sulfamyl; and

wherein R^4 is selected from halo, alkoxy and alkynyloxy;

or a pharmaceutically-acceptable salt thereof.

Compounds of Formula I would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of Formula I would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such compounds of Formula I would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns and dermatitis. Compounds of Formula I also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention of colorectal cancer. Compounds of Formula I would be useful in treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, conjunctivitis, swelling occurring after injury, myocardial ischemia, and the like. The compounds are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. Besides being useful for human treatment, these compounds are also useful for treatment of mammals, including horses, dogs, cats, rats, mice, sheep, pigs, etc.

The present compounds may also be used in co-therapies, partially or completely, in place of other conventional antiinflammatories, such as together with steroids, NSAIDs, 5-lipoxygenase inhibitors, LTB_4 inhibitors and LTA_4 hydrolase inhibitors.

The present invention preferably includes compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1 and do not significantly inhibit one or more other arachidonic pathway steps, such as thromboxane B_2 (TXB_2) production.

Preferably, the compounds have a cyclooxygenase-2 IC_{50} of less than about 0.1 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 0.5 μM, and more preferably of greater than 5 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

A preferred class of compounds consists of those compounds of Formula I wherein R^1 is lower haloalkyl; wherein R^2 is aryl selected from phenyl, naphthyl and biphenyl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, lower alkyl, cyano, carboxyl, lower alkoxycarbonyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, arylamino, nitro, halo, lower alkoxy and lower alkylthio; wherein R^3 is phenyl substituted at a substitutable position with a radical selected from lower alkylsulfonyl and sulfamyl; and

wherein R^4 is selected from halo, lower alkoxy and lower alkynyloxy; or a pharmaceutically-acceptable salt thereof.

A more preferred class of compounds consists of those compounds of Formula I wherein R^1 is lower haloalkyl; wherein R^2 is phenyl optionally substituted at a substitutable position with one or more radicals independently selected from lower alkyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, halo, lower alkoxy and lower alkylthio; wherein R^3 is phenyl substituted at a substitutable position with a radical selected from lower alkylsulfonyl and sulfamyl; and wherein R^4 is selected from halo, lower alkoxy and lower alkynyloxy; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula I wherein R^1 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl; wherein R^2 is phenyl optionally substituted at a substitutable position with one or more radicals independently selected from methyl, ethyl, isopropyl, butyl, *tert*-butyl, isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, trifluoromethoxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, fluoro, chloro, bromo, methoxy, methylenedioxy, ethoxy,

propoxy, n-butoxy, ethylthio, butylthio, hexylthio and methylthio; wherein R^3 is phenyl substituted at a substitutable position with a radical selected from methylsulfonyl and sulfamyl; and wherein R^4 is selected from fluoro, chloro, bromo, methoxy, ethoxy, propoxy, n-butoxy, 2-propynyloxy and 3-butynyloxy; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as follows:

5-(4-fluorophenyl)-4-[(4-methylsulfonyl)phenyl]-2-propoxy-6-trifluoromethylpyridine;

2-butoxy-5-(4-fluorophenyl)-4-[(4-methylsulfonyl)phenyl]-6-trifluoromethylpyridine;

2-(3-butynyloxy)-5-(4-fluorophenyl)-4-[(4-methylsulfonyl)phenyl]-6-trifluoromethylpyridine;

2-fluoro-5-(4-fluorophenyl)-4-[(4-methylsulfonyl)phenyl]-6-trifluoromethylpyridine;

5-(4-fluorophenyl)-2-methoxy-4-[(4-methylsulfonyl)phenyl]-6-trifluoromethylpyridine;

2-ethoxy-5-(4-fluorophenyl)-4-[(4-methylsulfonyl)phenyl]-6-trifluoromethylpyridine;

2-bromo-5-(4-fluorophenyl)-4-[(4-methylsulfonyl)phenyl]-6-trifluoromethylpyridine;

5-(4-fluorophenyl)-4-[(4-methylsulfonyl)phenyl]-2-propynyloxy-6-trifluoromethylpyridine;

4-[5-(4-fluorophenyl)-2-propoxy-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;

4-[2-butoxy-5-(4-fluorophenyl)-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;

4-[2-(3-butynyloxy)-5-(4-fluorophenyl)-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;

4-[2-fluoro-5-(4-fluorophenyl)-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-methoxy-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;
4-[2-ethoxy-5-(4-fluorophenyl)-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;
4-[2-bromo-5-(4-fluorophenyl)-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;
4-[5-(4-fluorophenyl)-2-(2-propynyloxy)-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;

2-methoxy-5-(4-methylphenyl)-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;
5-(4-ethylphenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;
2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-5-(4-trifluoromethylphenyl)-pyridine;
5-(4-hydroxyphenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;
5-(4-hydroxymethylphenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;
2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-5-(4-trifluoromethoxyphenyl)-pyridine;
5-(4-aminophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;
5-(4-chlorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;
5-(4-bromophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;
2-methoxy-5-(4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;
2-methoxy-4-[4-(methylsulfonyl)phenyl]-5-(4-methylthiophenyl)-6-trifluoromethyl-pyridine;

2-methoxy-5-(4-methylsulfinylphenyl)-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;

5-(4-cyanophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;

2-methoxy-5-(4-N-methylaminophenyl)-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;

4-[2-methoxy-5-(4-methylphenyl)-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[5-(4-ethylphenyl)-2-methoxy-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[2-methoxy-6-trifluoromethyl-5-(4-trifluoromethylphenyl)-pyridin-4-yl]benzenesulfonamide;

4-[5-(4-hydroxyphenyl)-2-methoxy-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[5-(4-hydroxymethylphenyl)-2-methoxy-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[2-methoxy-5-(4-trifluoromethoxyphenyl)-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[5-(4-aminophenyl)-2-methoxy-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-2-methoxy-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[5-(4-bromophenyl)-2-methoxy-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[2-methoxy-5-(4-methoxyphenyl)-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

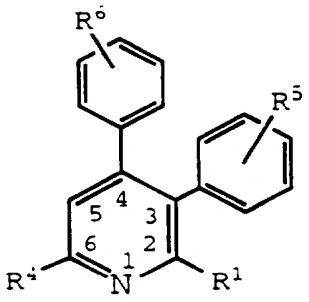
4-[2-methoxy-5-(4-methylthiophenyl)-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[2-methoxy-5-(4-methylsulfinylphenyl)-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[5-(4-cyanophenyl)-2-methoxy-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide; and

4-[2-methoxy-5-(4-N-methylaminophenyl)-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide.

Within Formula I there is a subclass of compounds of high interest represented by Formula II:



(II)

wherein R^1 is haloalkyl; wherein R^4 is selected from halo, alkoxy and alkynyloxy; wherein R^5 is halo; and wherein R^6 is alkylsulfonyl; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds consists of those compounds of Formula II wherein R^1 is lower haloalkyl; wherein R^4 is selected from halo, lower alkoxy and lower alkynyloxy; wherein R^5 is halo; and wherein R^6 is lower alkylsulfonyl; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula II wherein R^1 is trifluoromethyl; wherein R^4 is selected from fluoro, chloro, bromo, iodo, methoxy, ethoxy, isopropoxy, *tert*-butoxy, propoxy, butoxy, isobutoxy, pentoxy, 2-propynyloxy, and 3-butynyloxy; wherein R^5 is fluoro, chloro, bromo, iodo; and wherein R^6 is methylsulfonyl; or a pharmaceutically-acceptable salt thereof.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical. Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. The term "alkynyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkynyl" radicals having two to about six carbon atoms. Examples of alkynyl radicals include 2-propynyl, 3-butynyl and 2-butynyl. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include

fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "cycloalkoxy" embraces radicals having cycloalkyl radicals, as defined above, attached to an alkoxy radical. The term "alkynyloxy" embraces radicals having alkynyl portions of two to about ten carbon atoms attached to an oxygen atom. More preferred alkynyloxy radicals are

"lower alkynyloxy" radicals having two to six carbon atoms. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. The term "heterocyclic" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms[e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo[1,5-b]pyridazinyl,

etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclic group" may have 1 to 3 substituents such as lower alkyl, hydroxy, oxo, amino and lower alkylamino. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals

having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denotes NH_2O_2S-. The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$. The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes -(C=O)-. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Examples of such "alkoxycarbonyl" ester radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The term "alkylamino" denotes amino groups which have been substituted with one or two alkyl radicals. Suitable "alkylamino" may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "arylamino" denotes

amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical.

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formula I in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of treating inflammation or inflammation-associated disorders in a subject, the method comprising administering to the subject having such inflammation or disorder a therapeutically-effective amount of a compound of Formula I.

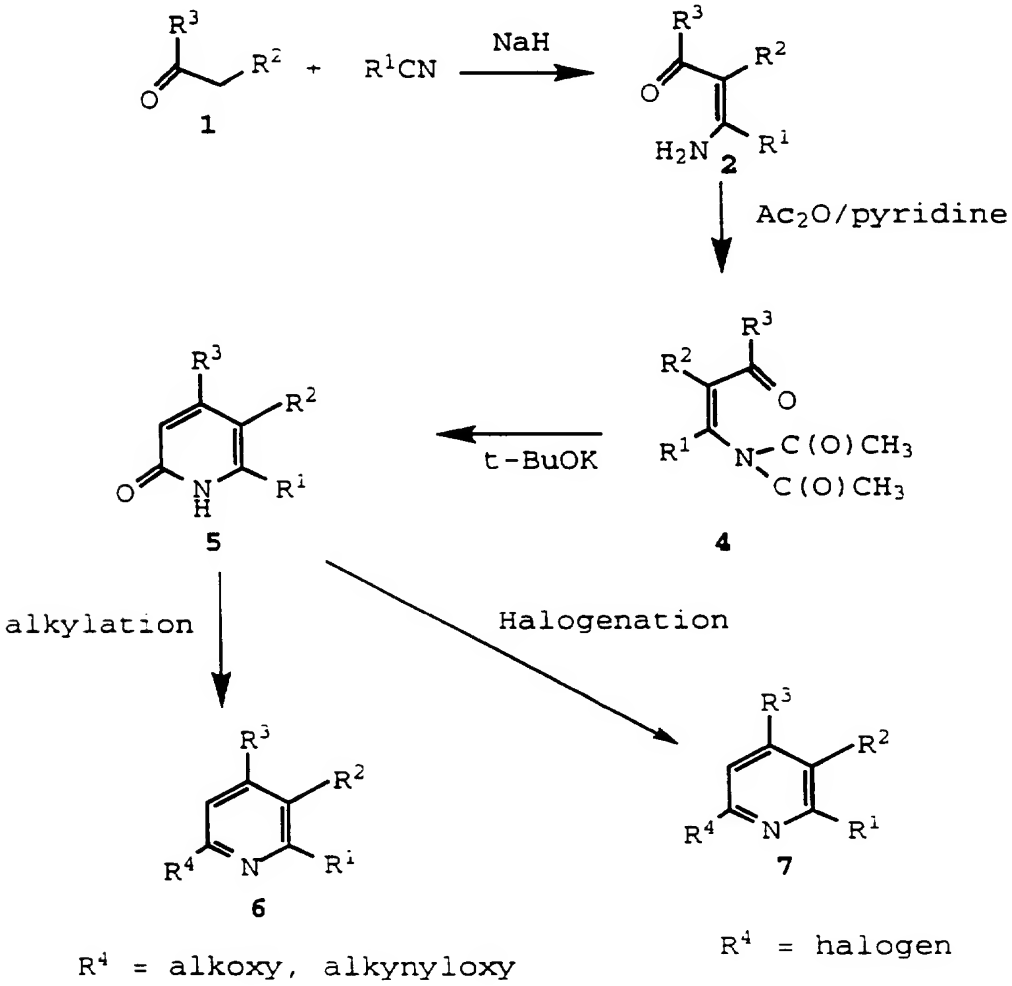
Also included in the family of compounds of Formula I are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric,

ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicyclic, salicyclic, *p*-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, salicyclic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

GENERAL SYNTHETIC PROCEDURES

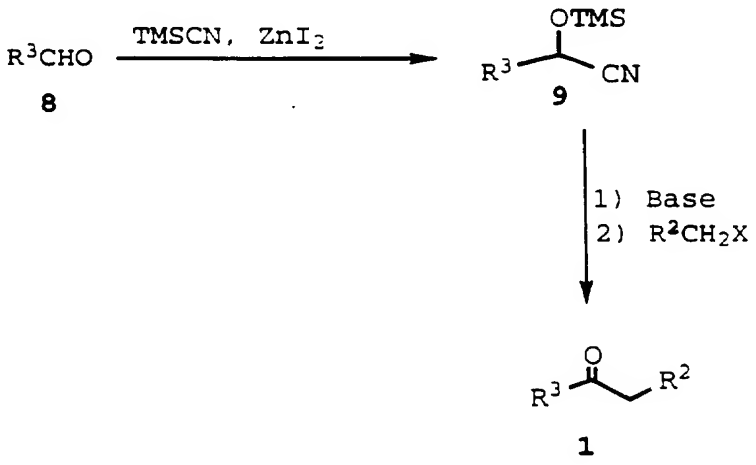
The compounds of the invention can be synthesized according to the following procedures of Schemes I-IV, wherein the R^1-R^6 substituents are as defined for Formula I-II, above, except where further noted.

Scheme I



Scheme I shows the multi-step method to form the 3,4-substituted pyridines **6** and **7** of the current invention. The compounds of this invention can be prepared from 1,2-diarylethanones as prepared by a procedure similar to the that described in U.S. patent 3,647,858. Reaction of diarylethanone **1** with sodium hydride and an activated nitrile, such as gaseous trifluoroacetonitrile, gives a mixture of enaminoketone **2** and 4,5-diarylpyrimidine. Reaction of **2** with excess acetic anhydride and pyridine yields *N,N*-diacetylenaminoketone **4**. Cyclization of **4** with potassium *tert*-butoxide in THF produces 4,5-diaryl-2-pyridone **5**. Pyridone **5** can be alkylated with an alkyl or alkynyl halide (R^4X) to give 2-alkoxypyridines **6**. Halogenation of **5** with a phosphorus oxyhalide (POX_3) or a phosphorus pentahalide (PX_5) yields the 2-halopyridines **7**.

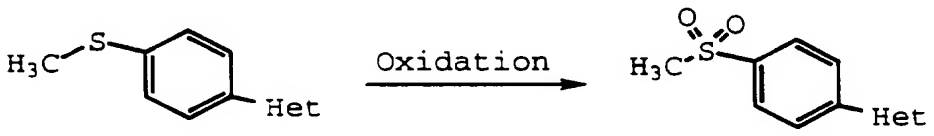
Scheme II



Scheme II shows a three step method of forming diarylethanone **1** for use in Synthetic Scheme I. In step

1, a silylating agent, such as trimethylsilyl cyanide, is added to a solution of substituted aldehyde **8** (R^3CHO) in a solvent such as dichloromethane. After the addition is complete, zinc iodide is added to give the protected ketone **9**. In step 2, the protected ketone **9** is added to a solution of base such as an alkyllithium reagent (i.e. lithium bis(trimethylsilyl)amide) in an appropriate solvent such as tetrahydrofuran. In step 3, a solution of the halo compound (where X is halo) in an appropriate solvent, such as tetrahydrofuran, is added. Aqueous hydrochloric acid is added to yield the ketone **1**.

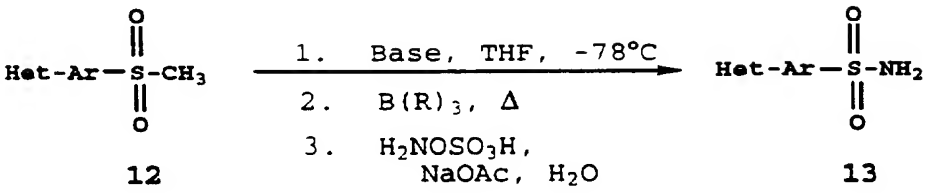
Scheme III



10 **11**

Scheme III shows a method to form the alkylsulfonylphenyl substituted pyridines **11** of the current invention by oxidation of alkylthio or alkylsulfinyl derivatives **10**. Aqueous hydrogen peroxide (30%) is added to a suspension of a (methylthio)phenyl substituted pyridine **10** in acetic acid. The mixture is stirred while heating to about 100°C to yield the sulfone **11**. Alternatively, meta-chloroperoxybenzoic acid (MCPBA), and other oxidizing agents can be used to form sulfones **11**.

Scheme IV

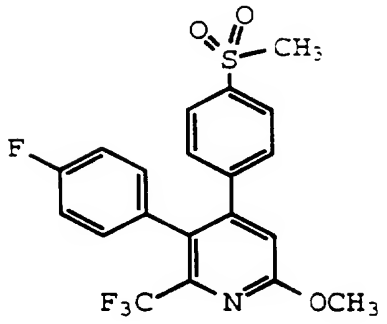


12 13

Synthetic Scheme IV shows the three step procedure used to prepare sulfonamide antiinflammatory agents **13** from their corresponding methyl sulfones **12**. In step one, THF solutions of the methyl sulfones **12** at -78°C are treated with an alkyllithium reagent, e.g., methyllithium, n-butyllithium, etc. In step two, the anions generated in step one are treated with an organoborane, e.g., triethylborane, tributylborane, etc., at -78°C then allowed to warm to ambient temperature prior to stirring at reflux. In step three, an aqueous solution of sodium acetate and hydroxylamine-O-sulfonic acid is added to provide the corresponding sulfonamide antiinflammatory agents **13** of this invention.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formula I-II. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated. All compounds showed NMR spectra consistent with their assigned structures.

Example 1



5-(4-Fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine

Step 1: Preparation of 2-(4-fluorophenyl)-1-[4-(methylthio)phenyl]ethanone

As described in U.S. Patent No. 3,647,858, a mixture of 4-methylthiophenylacetic acid (13.8 g, 0.076 ml) and 30 ml of thionyl chloride was held at reflux for 1.5 hours and concentrated. To this residue was added an additional 30 ml of thionyl chloride and the mixture was held at reflux for 3 hours and reconcentrated. The residue was dissolved in carbon disulfide (150 ml) and treated with fluorobenzene (14.8 g, 0.15 ml), followed by aluminum chloride (21.8 g, 0.17 ml) and stirred for 18 hours. The mixture was concentrated *in vacuo*. The residue was treated with ice water causing HCl evolution and formation of a solid. The solid was dissolved in methylene chloride, dried and concentrated. The residue was washed with ether and with sat. $NaHCO_3$, and filtered. The insoluble solid was dissolved in chloroform and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The

residue was recrystallized from chloroform/hexane to yield 2.91 g of tan solid.

Step 2: Preparation of 3-amino-2-(4-fluorophenyl)-1-[4-(methylthio)phenyl]-4,4,4,-trifluoro-2-butenone

To a mixture of 1.56 g (0.052 mole) of 80% sodium hydride oil dispersion, and 20 mL of anhydrous dimethylformamide (DMF) was added a solution of 13 g (0.05 mole) of 2-(4-fluorophenyl)-1-[4-(methylthio)phenyl]ethanone from Step 1 in 80 mL of anhydrous in 20 minutes. The resulting yellow solution was cooled to 0-5°C. To this solution was passed 11 g (0.12 mole) of gaseous trifluoroacetonitrile in 20 minutes. The reaction mixture was poured into water and extracted with methylene chloride. The methylene chloride extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give a semi-solid. This semisolid was heated with 10% ethyl acetate-hexane and filtered to recover 4.0 g (31%) of the starting ketone. The filtrate was concentrated and the residue was crystallized from 10% ethyl acetate-hexane to give 3.78 g (21%) of the desired product. A portion of this material was further purified by HPLC (10% ethyl acetate-hexane) to give 2.0 g of pure material, mp 122.5-124.5 °C. The mother liquor was concentrated and the residue was further purified by HPLC. The first fraction was 3.28 g (15%) of 2,4-bis(trifluoromethyl)-6-(4-fluorophenyl)-5-[4-(methylthio)phenyl]pyrimidine. The second fraction was additional 3.25 g (19%) of the desired product.

Step 3: Preparation of 3-(*N,N*-diacetylamino)-2-(4-fluorophenyl)-1-[4-(methylthio)phenyl]-4,4,4,-trifluoro-2-butenone

A mixture of 4.73 g of the ketone of Step 2, 29 g of acetic anhydride and 2.3 g (0.029 mole) of pyridine was held at reflux for 8 hours and concentrated *in vacuo* to remove excess acetic anhydride and pyridine to give the crude protected amino ketone which was used in the next step.

Step 4: Preparation of 5-(4-fluorophenyl)-4-[4-(methylthio)phenyl]-6-(trifluoromethyl)-2-oxy-pyridine

To a solution of the amino ketone of Step 3 in 20 mL of dry THF was added 3.8 g (0.034 mole) of potassium *tert*-butoxide causing an exotherm. The reaction mixture was held at reflux for 30 minutes and was let stand overnight. The reaction mixture was poured into 50 mL of 3 N HCl and extracted with ether. The ether extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residual solid was heated with methylene chloride, cooled and filtered to give 2.53 g (53%) of a light yellow solid: mp 221-224°C.

Step 5: Preparation of 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-2-oxo-pyridine

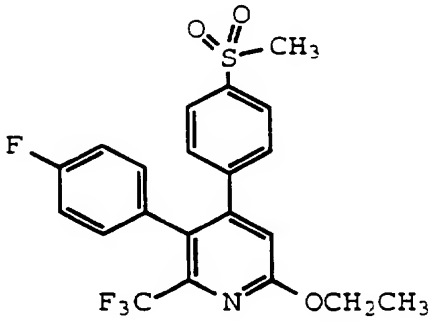
To a solution of 2.05 g (1.37 mMol) of the oxy-pyridine of Step 4 in 20 mL of glacial acetic acid was added 2.4 g (21 mMol) of 30% hydrogen peroxide. The reaction mixture was heated at 60°C for 1 hour and at 80°C

for 6 hours. The mixture was poured into water solution containing 6 g of sodium sulfite. The insoluble tan solid was filtered and air dried to give 2.05 g of solid: mp 232-242°C.

Step 6: Preparation of 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine

A mixture of 0.16 g (0.39 mMol) of the sulfone of Step 5, 0.2 g of potassium carbonate and 4.0 g of iodomethane, and 5 mL of DMF was stirred for 3 hours, poured into water and extracted with ether. The ether extract was washed with brine, dried over $MgSO_4$ and filtered through silica gel. The filtrate was concentrated *in vacuo* and the residue was crystallized from hexane to give 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine as a white solid (0.17 g): mp 166.5-168 °C.

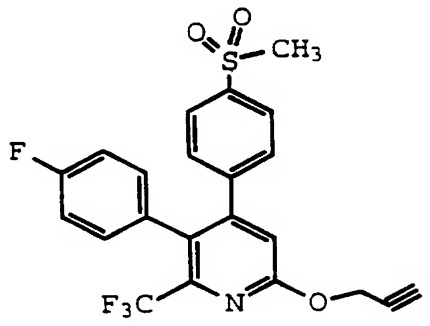
Example 2



2-Ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine

A mixture of 0.11 g of 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-2-oxo-pyridine (step 5 of Example 1), 3.3 g of bromoethane, 0.2 g of potassium carbonate, and 5 mL of dimethyl formamide (DMF) was stirred for 20 hours and concentrated *in vacuo*. The residue was triturated with water and extracted with methylene chloride. The methylene chloride extract was dried over $MgSO_4$ and filtered through silica gel. The filtrate was reconcentrated *in vacuo* and the residue was crystallized from methylene chloride/hexane to give 31 mg of solid: mp 168.5-170.5°C.

Example 3

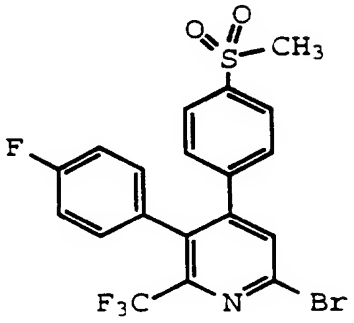


5-(4-Fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine

A mixture of 0.11 g of 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-2-oxo-pyridine (step 5 of Example 1), 2.5 g of propargyl bromide, 0.3 g of potassium carbonate, and 5 mL of DMF was stirred for 60 hours and concentrated *in vacuo*. The residue was triturated with water and extracted with methylene chloride. The methylene chloride extract was dried over $MgSO_4$ and filtered through silica gel. The filtrate was

reconcentrated *in vacuo* and the residue was crystallized from ether/hexane to give 56 mg of white solid: mp 138-139°C.

Example 4



2-Bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine

A mixture of 0.35 g of 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-2-oxo-pyridine (step 5 of Example 1), 3 g of phosphorus pentabromide, 0.3 g of potassium bromide and 10 mL of 1,2-dichlorobenzene was held at reflux for 2 hours. The reaction mixture was cooled. An addition 3.7 g of phosphorus pentabromide was added to the reaction mixture and the reaction mixture was held at 90°C for 8 hours, and at 180-190°C for 2 days. The reaction mixture was cooled and stirred with water and methylene chloride. The methylene chloride layer was dried over $MgSO_4$ and filtered through silica gel. The methylene chloride filtrate was concentrated *in vacuo* and the residue was purified by HPLC (20% ethyl acetate/hexane then 50% ethyl acetate/hexane). The fraction eluted with 50% ethyl acetate/hexane yielded a solid.

Recrystallization from methylene chloride/hexane yielded 150 mg of white solid: mp 187.5-189°C.

BIOLOGICAL EVALUATION

Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test was performed with materials, reagents and procedures essentially as described by Winter, et al., (*Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962)). Male Sprague-Dawley rats were selected in each group so that the average body weight was as close as possible. Rats were fasted with free access to water for over sixteen hours prior to the test. The rats were dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline was administered and the volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a group of drug-treated animals was compared with that of a group of placebo-treated animals and the percentage inhibition of edema was determined (Otterness and Bliven, Laboratory Models for Testing NSAIDs, in Non-steroidal Anti-Inflammatory Drugs (J. Lombardino, ed. 1985)). The % inhibition shows the % decrease from control paw volume determined in this procedure and the data for selected compounds in this invention are summarized in Table I.

TABLE I.

RAT PAW EDEMA

% Inhibition

@ 20mg/kg body weight

Example 1	12

Evaluation of COX-1 and COX-2 activity *in vitro*

The compounds of this invention exhibited inhibition *in vitro* of COX-2. The COX-2 inhibition activity of the compounds of this invention illustrated in the Examples was determined by the following methods.

a. Preparation of recombinant COX baculoviruses

Recombinant COX-1 and COX-2 were prepared as described by Gierse et al, [*J. Biochem.*, **305**, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 was cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses were isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells ($2x10^8$) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant

viruses were purified by three rounds of plaque purification and high titer (10^7-10^8 pfu/ml) stocks of virus were prepared. For large scale production, SF9 insect cells were infected in 10 liter fermentors (0.5 x 10^6/ml) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio] -1-propanesulfonate (CHAPS). The homogenate was centrifuged at 10,000xG for 30 minutes, and the resultant supernatant was stored at -80°C before being assayed for COX activity.

b. Assay for COX-1 and COX-2 activity:

COX activity was assayed as PGE_2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme were incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 µM). Compounds were pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after ten minutes at 37°C/room temperature by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE_2 formed was measured by standard ELISA technology (Cayman Chemical). Results are shown in Table II.

TABLE II.

COX-1 murineCOX-2 murine

	ID_{50} μM	ID_{50} μM
Example		
1	.3	>30
2	.3	>30
3	.2	>30
4	.6	>100

Also embraced within this invention is a class of pharmaceutical compositions comprising one or more compounds of Formula I in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and composition may, for example, be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably between about 1 to 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

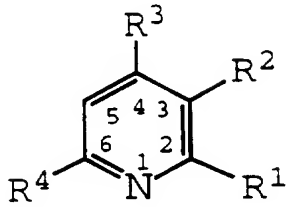
For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered<u>per os</u>, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions

may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What is claimed is:

1. A compound of Formula I



(I)

wherein R^1 is haloalkyl;

wherein R^2 is aryl optionally substituted at a substitutable position with one or more radicals independently selected from alkylsulfinyl, alkyl, cyano, carboxyl, alkoxycarbonyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, halo, alkoxy and alkylthio;

wherein R^3 is aryl substituted at a substitutable position with a radical selected from alkylsulfonyl and sulfamyl; and

wherein R^4 is selected from halo, alkoxy and alkynyloxy;

or a pharmaceutically-acceptable salt thereof.

2. Compound of Claim 1 wherein R^1 is lower haloalkyl; wherein R^2 is aryl selected from phenyl, naphthyl and biphenyl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, lower alkyl, cyano, carboxyl, lower alkoxycarbonyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, arylamino, nitro, halo, lower alkoxy and lower alkylthio; wherein R^3 is phenyl substituted at a substitutable position with a radical selected from

lower alkylsulfonyl and sulfamyl; and wherein R^4 is selected from halo, lower alkoxy and lower alkynyloxy; or a pharmaceutically-acceptable salt thereof.

3. Compound of Claim 2 wherein R^1 is lower haloalkyl; wherein R^2 is phenyl optionally substituted at a substitutable position with one or more radicals independently selected from lower alkyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, halo, lower alkoxy and lower alkylthio; wherein R^3 is phenyl substituted at a substitutable position with a radical selected from lower alkylsulfonyl and sulfamyl; and wherein R^4 is selected from halo, lower alkoxy and lower alkynyloxy; or a pharmaceutically-acceptable salt thereof.

4. Compound of Claim 3 wherein R^1 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl; wherein R^2 is phenyl optionally substituted at a substitutable position with one or more radicals independently selected from methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, trifluoromethoxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, fluoro, chloro, bromo, methoxy, methylenedioxy, ethoxy, propoxy, n-

butoxy, ethylthio, butylthio, hexylthio and methylthio; wherein R^3 is phenyl substituted at a substitutable position with a radical selected from methylsulfonyl and sulfamyl; and wherein R^4 is selected from fluoro, chloro, bromo, methoxy, ethoxy, propoxy, n-butoxy, 2-propynyloxy and 3-butynyloxy; or a pharmaceutically-acceptable salt thereof.

5. Compound of Claim 4 selected from compounds, and their pharmaceutically acceptable salts, of the group consisting of

5-(4-fluorophenyl)-4-[(4-methylsulfonyl)phenyl]-2-propoxy-6-trifluoromethylpyridine;

2-butoxy-5-(4-fluorophenyl)-4-[(4-methylsulfonyl)phenyl]-6-trifluoromethylpyridine;

2-(3-butynyloxy)-5-(4-fluorophenyl)-4-[(4-methylsulfonyl)phenyl]-6-trifluoromethylpyridine;

2-fluoro-5-(4-fluorophenyl)-4-[(4-methylsulfonyl)phenyl]-6-trifluoromethylpyridine;

5-(4-fluorophenyl)-2-methoxy-4-[(4-methylsulfonyl)phenyl]-6-trifluoromethylpyridine;

2-ethoxy-5-(4-fluorophenyl)-4-[(4-methylsulfonyl)phenyl]-6-trifluoromethylpyridine;

2-bromo-5-(4-fluorophenyl)-4-[(4-methylsulfonyl)phenyl]-6-trifluoromethylpyridine;

5-(4-fluorophenyl)-4-[(4-methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-trifluoromethylpyridine;

4-[5-(4-fluorophenyl)-2-propoxy-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;

4-[2-butoxy-5-(4-fluorophenyl)-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;

4-[2-(3-butynyloxy)-5-(4-fluorophenyl)-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;

4-[2-fluoro-5-(4-fluorophenyl)-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-methoxy-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;

4-[2-ethoxy-5-(4-fluorophenyl)-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;

4-[2-bromo-5-(4-fluorophenyl)-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-2-(2-propynyloxy)-6-trifluoromethylpyridin-4-yl]benzenesulfonamide;

2-methoxy-5-(4-methylphenyl)-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;

5-(4-ethylphenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;

2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-5-(4-trifluoromethylphenyl)-pyridine;

5-(4-hydroxyphenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;

5-(4-hydroxymethylphenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;

2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-5-(4-trifluoromethoxyphenyl)-pyridine;

5-(4-aminophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;

5-(4-chlorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;

5-(4-bromophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;

2-methoxy-5-(4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;

2-methoxy-4-[4-(methylsulfonyl)phenyl]-5-(4-methylthiophenyl)-6-trifluoromethyl-pyridine;

2-methoxy-5-(4-methylsulfinylphenyl)-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;

5-(4-cyanophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;

2-methoxy-5-(4-N-methylaminophenyl)-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl-pyridine;

4-[2-methoxy-5-(4-methylphenyl)-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[5-(4-ethylphenyl)-2-methoxy-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[2-methoxy-6-trifluoromethyl-5-(4-trifluoromethylphenyl)-pyridin-4-yl]benzenesulfonamide;

4-[5-(4-hydroxyphenyl)-2-methoxy-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[5-(4-hydroxymethylphenyl)-2-methoxy-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[2-methoxy-5-(4-trifluoromethoxyphenyl)-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[5-(4-aminophenyl)-2-methoxy-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-2-methoxy-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[5-(4-bromophenyl)-2-methoxy-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[2-methoxy-5-(4-methoxyphenyl)-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

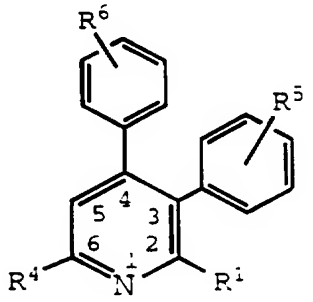
4-[2-methoxy-5-(4-methylthiophenyl)-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[2-methoxy-5-(4-methylsulfinylphenyl)-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide;

4-[5-(4-cyanophenyl)-2-methoxy-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide; and

4-[2-methoxy-5-(4-N-methylaminophenyl)-6-trifluoromethyl-pyridin-4-yl]benzenesulfonamide.

6. A compound of Formula II



(II)

wherein R^1 is haloalkyl; wherein R^4 is selected from halo, alkoxy and alkynyloxy; wherein R^5 is halo; and wherein R^6 is alkylsulfonyl; or a pharmaceutically-acceptable salt thereof.

7. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 1; or a pharmaceutically-acceptable salt thereof.

8. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 2; or a pharmaceutically-acceptable salt thereof.

9. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 3; or a pharmaceutically-acceptable salt thereof.

10. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 4; or a pharmaceutically-acceptable salt thereof.

11. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 5; or a pharmaceutically-acceptable salt thereof.

12. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to such inflammation or inflammation-associated disorder, a therapeutically-effective amount of a compound of Claim 1; or a pharmaceutically-acceptable salt thereof.

13. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to such inflammation or inflammation-associated disorder, a therapeutically-effective amount of a compound of Claim 2; or a pharmaceutically-acceptable salt thereof.

14. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to such inflammation or inflammation-associated disorder, a therapeutically-effective amount of a compound of Claim 3; or a pharmaceutically-acceptable salt thereof.

15. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to such inflammation or inflammation-associated disorder, a therapeutically-effective amount of a compound of Claim 4; or a pharmaceutically-acceptable salt thereof.

16. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having such inflammation or inflammation-associated disorder, a therapeutically-effective amount of a compound of Claim 5; or a pharmaceutically-acceptable salt thereof.

17. The method of Claim 12 for use in treatment of inflammation.

18. The method of Claim 12 for use in treatment of an inflammation-associated disorder.

19. The method of Claim 18 wherein the inflammation-associated disorder is arthritis.

20. The method of Claim 18 wherein the inflammation-associated disorder is pain.

21. The method of Claim 18 wherein the inflammation-associated disorder is fever.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 96/01110

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/64 C07D213/61 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB,A,1 238 959 (MERCK & CO.) 14 July 1971 cited in the application see claims; example 34	1-21
A	US,A,4 011 328 (PINHAS HENRI ET AL) 8 March 1977 cited in the application see the whole document	1-21

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 May 1996	04.06.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Bosma, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

1. national application No.
PCT/US96/01110

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 12-21 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/US 96/01110

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A-1238959	14-07-71	AT-A,B	306016	15-02-73
		AT-A,B	306017	15-02-73
		AT-A-	296987	15-02-72
		AT-A-	295533	15-12-71
		BE-A-	724667	29-05-69
		DE-A-	1810822	07-08-69
		FR-M-	8423	10-06-71
		FR-A-	1593806	01-06-70
		GB-A-	1238960	14-07-71
		NL-A-	6816241	03-06-69
		US-A-	3715358	06-02-73
US-A-4011328	08-03-77	FR-A-	2248027	16-05-75